ASX ANNOUNCEMENT

Actinogen announces positive Alzheimer's Disease clinical results

Sydney, 10 October 2022. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce positive Phase 2a clinical data from its Alzheimer's Disease (AD) biomarker study, which validates the Company's Xanamem® program.

Key efficacy conclusions:

- **The analysis validates and significantly de-risks the Actinogen Xanamem program by showing:**
  - **Clinical activity of Xanamem in biomarker-positive AD patients**
  - **Large clinical effect size**
  - **Utility of blood pTau[1] levels to select suitable patients for next Phase 2b AD trial**
  - **Utility of FDA-recognized Clinical Dementia Rating - Sum of Boxes (CDR-SB) to measure the benefit of Xanamem in future trials**
  - **Complements positive prior trial findings on cognition.**

Key clinical features and outcomes:

- **Phase 2a placebo-controlled trial was re-run in biomarker-positive patients using available blood biomarker levels in 72 patients from the prior XanADu study of 185 patients with mild AD**
- **Used a pre-specified analysis plan to avoid bias**
- **Patients with elevated blood pTau showed a clinically significant Xanamem effect on the CDR-SB endpoint plus trends in a Neurologic Test Battery (NTB) and the Mini Mental State Exam (MMSE)**
- **CDR-SB effect of 0.6 - 0.8 points is larger than the 0.45 points reported recently for the anti-amyloid antibody lecanemab and represents a 60% reduction in progression over 12 weeks compared with placebo (lecanemab reported to show 27% over 18 months)[2]**
- **Regulatory path to approval is clear and uncontroversial with CDR-SB**
- **Findings significantly de-risk and improve AD program efficiency**
- **CDR-SB will be a primary endpoint in the upcoming Phase 2b trial.**

® Xanamem is a registered trademark of Actinogen Medical Limited

[1] Tau is a brain protein and phosphorylated Tau (pTau) is an Alzheimer's Disease diagnostic biomarker

[2] https://www.eisai.com/news/2022/news202271.html 28 September 2022

Biomarker study results in brief

The new clinical results show that Xanamem had a therapeutic effect in patients with a biomarker-positive blood profile, indicated by an elevated level of the pTau biomarker. Elevated blood pTau is regarded as a promising method to identify patients with the AD type of dementia likely to progress to more severe disease.[2]

Positive effect seen on the CDR-SB, which is a well-recognized primary endpoint for trials in patients with early-stage AD, means that use of this endpoint in future trials will be straightforward and uncontroversial. The size of the effect seen with Xanamem is considerably greater than that reported for anti-amyloid antibodies.

A blood test for pTau is also a more practical and efficient method to choose patients with AD for clinical trials compared to more complicated brain scans.

Eminent world-leading authority on dementia, Associate Professor Michael Woodward, commented:

"The positive data for CDR-SB and other endpoints are encouraging and indicate a likely therapeutic effect of Xanamem in patients with the early stages of AD. The use of pTau blood levels to confirm the diagnosis of AD in future trials represents a practical and efficient method to select patients at risk of disease progression and in whom a treatment effect is more likely to be observed."

Professor Paul Rolan, Actinogen's Chief Medical Officer, said:

"These clinical results provide further validation of our Alzheimer's Disease program and are a significant step forward in the development of Xanamem as a new treatment for Alzheimer's Disease with a novel, amyloid-independent mechanism of action."

Dr Steven Gourlay, Actinogen's CEO and MD, said:

"We are very pleased to see such positive clinical data for patients with biomarker-positive, mild Alzheimer's Disease. The results extend findings of therapeutic effects on cognition in two prior trials of cognitively normal, older volunteers to patients with early Alzheimer's Disease. The data also validate the dose range planned for our upcoming trials in Alzheimer's Disease and Depression.

"Xanamem has the potential to be a novel daily oral therapy for Alzheimer's Disease and other conditions that could be safely used alone or in combination with other therapies. The results affirm our confidence in the upcoming clinical trials that will confirm if Xanamem can make a significant improvement in the lives of patients and their families living with serious neurological and psychiatric conditions."

Biomarker study results in detail

The biomarker study was conducted in 72 patients with available blood biomarker samples from the prior Phase 2a placebo-controlled XanADu study of 185 patients. Patients had a clinical diagnosis of mild AD, with a MMSE score of 20 to 26 and were treated with Xanamem 10 mg or placebo once daily for 12 weeks. The trial was conducted in the US, UK and Australia. The average age of patients was 71 years, 57% were female and baseline mean CDR-SB score was 3.9.[3]

[2] Thijssen E et al. 2020 Diagnostic value of plasma phosphorylated pTau181 in Alzheimer's Disease and Frontotemporal Lobar Degeneration

[3] Biomarker study: Baseline mean CDR-SB of 3.9 (with 1.6-point standard deviation); original XanADu study mean was 3.8 (SD 1.7)

Study goals

The goals of the study were to:

1. measure Xanamem effects in patients with biomarker-positive AD by excluding the 'noise' from patients with other types of dementia who were unlikely to progress during the trial, and
2. establish if there was any short-term effect of Xanamem on the levels of blood biomarkers themselves. A short-term effect of Xanamem on protein biomarkers was considered unlikely because its mechanism is not via direct action on amyloid and tau proteins in the brain.

Analytical & statistical methodologies

The analysis was 'double-blind' and 'pre-specified' meaning the results were generated according to an analysis plan where the biomarker laboratory and company personnel were unaware of which treatment patients had used. This method is standard in the biopharmaceutical industry to avoid bias in the results.

Standard statistical methods were 'least squares' (LS) mean calculations of change during treatment compared to placebo along with a calculation of the *Cohen's d* statistic of effect size for treatment compared to placebo, which compares change to baseline variability (standard deviation).

Biomarker samples were analyzed by a leading AD blood biomarker laboratory in Gothenburg, Sweden.[4] There were sufficient sample volumes for analysis of pTau, amyloid beta 42 & 40 and glial fibrillary acidic protein (GFAP).

Analysis examined the protocol-specified clinical endpoints for clinically significant effects overall and by four target subgroups potentially defining patients more likely to have pathologic AD: pTau above the median vs. below, pTau > 10.2 pg/mL vs. below, amyloid ratio above the median vs. below and MMSE score of 20-23 vs. 24-26.

Findings

The primary finding of the study was that blood pTau levels above the median value of 6.74 pg/mL (n=34) or 10.2 pg/mL (n=9) identified patients who had a clinically significant therapeutic benefit from Xanamem with an average effect size of 0.6 to 0.8 points on the CDR-SB scale, measuring cognition and function, which is widely used in modern trials of early-stage AD (Cohen's d = 0.41, p = 0.09).

This effect size represents a 60% reduction in progression compared with placebo treatment. Based on CDR-SB scores, twice as many patients in the Xanamem group were stable or improved compared with those in the placebo group.

The findings confirm that the CDR-SB is a suitable endpoint for measuring Xanamem's therapeutic effect in trials of biomarker-positive AD patients over a period as short as 12 weeks. The ratio of amyloid beta 42:40 did not identify patients responsive the therapy.

In the elevated pTau group, positive but less striking effects were also seen in the NTB which measures 'executive function' (Cohen's d = 0.26), and MMSE which is a 'bedside test' measuring cognition (Cohen's d = 0.16).

The low MMSE group was examined to see if more severe patients in the trial derived measurable clinical benefit from Xanamem, without consideration of biomarker classification - meaning that it consisted of a mixed group of AD (biomarker positive) and non-AD type dementia (biomarker negative). It showed a statistically and clinically significant treatment benefit on the MMSE score of 2 units (Cohen's d 0.93, p = 0.02), without effect on other endpoints.

[4] Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, The Sahlgrenska University, Gothenburg, Sweden

Minor changes in levels of pTau, a ratio of amyloid beta 42:40 and GFAP were observed in both Xanamem and placebo groups within the test-retest boundaries of assay 'noise' meaning that no differences were seen between treatments over 12 weeks. This finding is consistent with the non-amyloid mechanism of Xanamem. While potential biomarker measures of disease-modification will be examined in longer clinical trials, the primary determinant of disease modification will be durable effects on clinical endpoints such as the CDR-SB.

As seen in the original trial analysis (publication pending), patients in both Xanamem and placebo groups saw no improvement or worsening in the original trial's co-primary endpoints of ADAS-Cog14[5] or ADCOMS,[6] confirming the lack of utility of these endpoints for a short, 12-week trial in the early-stage AD patients studied.

Webcast

Actinogen CEO Dr Steven Gourlay and CMO Professor Paul Rolan will present a webcast at **11am AEDT today** to review the biomarker study results as set out in an investor presentation released in a separate announcement to the ASX this morning.

Register for the webcast by clicking on the link below or pasting the address into a browser:

https://us02web.zoom.us/webinar/register/WN__5Yufq4xQ4-upem9WPnHwQ

A full recording of the webcast will be made available on the Actinogen website www.actinogen.com.au as soon as practicable following the conclusion of the webcast.

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Announcement authorised by the Board of Directors of Actinogen Medical

About Actinogen Medical

Actinogen Medical (ACW) is an ASX-listed, biotechnology company developing a novel therapy for neurological and neuropsychiatric diseases associated with dysregulated brain cortisol. There is a strong association between cortisol and detrimental changes in the brain, affecting cognitive function, harm to brain cells and long-term cognitive health.

Cognitive function means how a person understands, remembers and thinks clearly. Cognitive functions include memory, attention, reasoning, awareness and decision-making.

Actinogen is currently developing its lead compound, Xanamem, as a promising new therapy for Alzheimer's Disease and Depression and hopes to study Fragile X Syndrome and other neurological and psychiatric diseases in the future. Reducing cortisol inside brain cells could have a positive impact in these and many other diseases. The cognitive dysfunction, behavioural abnormalities, and neuropsychological burden associated with these conditions is debilitating for patients, and there is a substantial unmet medical need for new and improved treatments.

[5] AD Assessment Scale - Cognitive
[6] AD Composite Score

About Xanamem

Xanamem's novel mechanism of action is to block the production of cortisol inside cells through the inhibition of the 11β-HSD1 enzyme in the brain. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing its capsule.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease, and Xanamem has shown the ability to enhance cognition in healthy, older volunteers. Cognitive impairment is also a feature in Depression and many other diseases. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 300 volunteers and patients, so far finding a statistically significant improvement in working memory and attention, compared with placebo, in healthy, older volunteers in two consecutive trials. Previously, high levels of target engagement in the brain with doses as low as 5 mg daily have been demonstrated in a human PET imaging study. A series of Phase 2 studies in multiple diseases is being conducted to further confirm and characterize Xanamem's therapeutic potential.

Xanamem is an investigational product and is not approved for use outside of a clinical trial by the FDA or by any global regulatory authority. Xanamem® is a trademark of Actinogen Medical.

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